DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 05/03/2011 has been entered.

At Applicants' request, an interview on the case was conducted 6/21/2011. An interview summary is attached to this Office action.

Claims 72-85 are under examination.

Claim Rejections - 35 USC § 112

Claims 82-85 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 82-85 are directed to the slowing of hair growth as a result of the administration of an aromatase inhibitor alone. This is New Matter. The specification discloses that hair growth is slowed by the concurrent inhibition of aromatase and 5-alpha-reductase (p. 34).

Claims 72-85 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright,* 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]
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> [1]As pointed out by the court in In re Angstadt, 537 F.2d 498 at 504 (CCPA 1976), the key word is “undue”, not “experimentation”.

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands',* 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman,* 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,

6) the relative skill of those in the art,
7) the predictability of those in the art,
8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. In re Fisher, 57 CCPA 1099, 1108,427 F.2d 833,839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands" factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

The invention relates to a method for stabilizing, increasing or restoring collagen by identifying a collagen deficient condition selected from the group consisting of wrinkles of the face, pregnancy strias and strias of the lower abdomen, thighs or buttocks by administering a steroidal aromatase inhibitor in an amount sufficient to alleviate at least one symptom of said collagen deficient condition. The invention also relates to slowing the growth of hair by administration of the aromatase inhibitor.

The relative skill of those in the art is high, generally that of a medical doctor or a PhD biochemist.

That factor is outweighed, however, by the unpredictable nature of the art. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher,* 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and

physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.,* 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain).

The prior art shows that loss of estrogen decreases collagen content in the skin and that augmentation of the skin with collagen increases collagen content. For example, Affinto et al. (previously cited) discusses a study that evaluated the effect of aging and postmenopausal hypoestrogenism on skin collagen content. It was demonstrated that in postmenopausal patients, there was a statistically significant decrease of percentage of skin collagen type I, type III and type III/type I ratio in comparison to pre-menopausal women. The observation correlated with chronological age. Affinito et al. conclude that the data suggests that the decrease of skin collagen is an estrogen-related phenomenon (abstract, page 241, right col., under “Results”, Figs 1-4 and page 246, right col.)

Brincat et al. (previously cited) evaluated skin collagen changes in post-menopausal women receiving oestradiol (estradiol) gel topically for one year. Skin

biopsies of the abdomen and the thigh demonstrated that abdominal collagen significantly increased while the increase in thigh collagen was not statistically significant (abstract and Fig. 1-3).

Varila et al. (previously cited) examined the effect of topical estradiol on skin collagen and elastin. Varila et al. observed that the application of topical estradiol increases the amount of skin collagen (abstract and "Results", page 986). Varila notes that the mechanical properties of the skin such as tensile strength are largely attributed to the collagen component (p. 988, right col. fourth paragraph).

Aromatase is an enzyme that produces estradiol which is converted into estrogen. Inhibition of aromatase will inhibit the formation of estrogen. The prior art discloses that estradiol, a product of aromatase catalysis of testosterone, supports the formation of collagen in the skin. Hence, the skilled artisan would reasonably expect that inhibition of aromatase would lead to a decrease in estrogen and result in a decrease in the amount of collagen in the skin, thus leading to wrinkles, etc. Hence, there is no way for one skill in the art to know, a priori, if a given inhibitor of aromatase can restore, increase or stabilize the amount of collagen in the skin of an individual a reasonable expectation of results. Thus, the state of the prior art does not support the broad scope of the above claims.

Regarding the effect of aromatase inhibitors on hair growth (claims 82-85), Messenger (US 6,020,327) teaches that a method for treating or preventing hair loss by administering an aromatase inhibitor to an area to be treated (col. 4, lines 32-46).

Thus, the prior art teaches the opposite effect to what is claimed. That is, aromatase inhibitors which decrease the amount of estradiol and thus estrogen would have a negative effect on collagen since the prior art demonstrates that estrogen supports collagen synthesis. Likewise, aromatase inhibitors stimulate or prevent hair growth.

2. The breadth of the claims

The claims are broad insofar as they disclose a method for stabilizing, increasing or restoring collagen in a subject suffering from wrinkles, pregnancy strias and strias of the lower abdomen, thighs or buttocks by the application of a steroidal aromatase inhibitor wherein the growth of hair is slowed.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification alleges that collagen and therefore skin tightness can be positively influenced in collagen-containing body parts by administering a steroidal aromatase inhibitor for inhibiting the production and/or the effect of estrogens (page 6, lines 14-21). The specification discloses that by means of biopsies it was found that the proportion of collagen fibers increased (page 7, lines9-11). The specification does not actually disclose what substance was applied and where it was applied to produce this outcome. A comparison of Figs. 1 and 2 allegedly shows that the proportion of the collagen fibers increases after application of (presumably) an inhibitor of aromatase. There is no description of what aspect of collagen the pictures represent. It is difficult to tell from the pictures what aspect of collagen is being shown. The specification does not

explain what the figures physically represent. It is difficult to tell from the pictures if there is an increase or decrease in the proportion of collagen fibers.

The specification provides three types of examples for the alleged support for the claims. Two examples are directed to the administration of oxidized soya glycines for wrinkles and strias and the third example is directed to the treatment of a tennis player having strong overstretching in the joints with Formestan, a known aromatase inhibitor.

The specification reports that there was an improvement in the appearance of the wrinkles and strias of the patient after the application of oxidized soya glycines (examples, 1 and 2). Although the claims are no longer directed to the administration of oxidized soya glycines, it is disclosed that oxidized soy a glycines have anti-aromatase actiivty which are responsible for the collagen augmentation. However, the nature of the oxidation of soya glycines is unclear. The specification cites two references regarding methods to carry out this process. An enzymatic method reported by Fujimoto is directed to the microbial degradation of the phytosterol chain of specific steroids. 3-oxo-24-ethylchoest-4-en-26-oic acid was converted into 3-oxochol-4-en-24-oic acid and androst-4-ene-3,17-dione. These conversions do not appear to be related to oxidation. The conversion to the dione suggests a reduction. Fujimoto discloses that they were unable to obtain workable quantities of the degradation product corresponding to 26-hydroxy-24-ethylcholest-4-ene. Thus, it is unclear if the microbial process results in any type of oxidation or if it is applicable to any possible steroid. Thus, Fujimoto does not support the concept that his method will oxidize sterols in soya glycines.

Regarding the chemical method reported by Welzel et al., the degradation of the steroid chain provides a ketone, so this is an oxidation but it is unclear if this is the reaction used to make oxidized soya glycines. Welzel teaches the production of androstenedione (compound 29). However, the specification fails to disclose how this relates to the structures of the unknown sterols allegedly isolated from soy glycines that have been subjected to oxidation. That is, since the structures of the sterols isolated from soya glycines are unknown, the skilled artisan would not know what compounds would be obtained from the treatment of said compounds by the method of Welzel et al. and if the resulting compounds would necessarily be inhibitors of aromatase.

Furthermore, the prior art does not support that sources of soya naturally decrease estrogen reduction. Islam et al. (2008) teaches that the administration of soy phytoestrogens may serve as an estrogenic analog in supporting the performance on some cognitive tasks when endogenous estrogen levels are low. Thus, soy phytosterols support estrogenic effects (p. 260, left col., 2nd paragraph under the heading of "discussion").

Thus, the examples relating to the administration of oxidized soya glycines to alleviate collagen deficiencies is not sufficient to support the concept that aromatase inhibitors are present therein and responsible for the effect. The specification does not disclose any support that would lead the skilled artisan to believe that the oxidation method of Welzel will somehow cause soy to have the opposite effect compared to the estrogen-positive effect that soy is known to have in the prior art. Thus, examples 1 and

2 do not correlate the improvement to an increase in collagen fibers to the inhibition of aromatase to produce the observed effect on wrinkles or strias.

The third example relates the administration of an known aromatase inhibitor, Formestan, to a person having overstretching of the tendons. The result of the administration is reduced pain and a feeling of stabilization of the joints of the knees. There is no correlation shown between anti-aromatase activity and pain reduction or the perceived stabilization effect. Alleviation of pain could be due to an anti-inflammatory effect. The stabilization effect is perceived and therefore subjective. It is unclear what a "feeling" means.

Thus, the disclosure of the specification does not support the claimed invention because it does not provide clear working examples that correlate an anti-aromatase activity to the improvement of collagen which is contrary to what is known in the prior art.

Regarding the claimed effect of slowing a subjects body hair growth, the specification teaches that this is a combined effect of simultaneous inhibition of 5-alpha-reductase and aromatase, not aromatase activity by itself (p. 34). As noted, Messenger teaches that inhibition of aromatase leads to an increase in hair growth. This is contrary to what is claimed. There are no working examples to support the claims of limiting hair growth. The instant disclosure is also contrary to what is known about the effect of inhibitors of aromatase and 5-alpha-reductase on hair growth. Pineda teaches that inhibitors of 5-alpha reductase increase hair follicle growth or prevent future hair follicle loss (section [0008]). The specification offers no working examples to direct the skilled

artisan how to slow hair loss by inhibition of aromatase alone or inhibition of aromatase and 5-alpha reductase.

4. The quantity of experimentation necessary

Because of the known nature of the art *supra* and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that one could be predictably stabilize, restore or increase collagen in skin or slow hair growth by the application of aromatase inhibitor as inferred in the claims and contemplated by the specification. Genentech Inc. vs. Nova Nordisk states, "[A] patent is not a hunting license. It is not a reward for a search but a compensation for its successful conclusion and 'patent protection' is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" (42 USPQ 2d 1001, Fed. Circuit 1997).

To practice the invention of the instant claims required undue experimentation due to the unpredictability and the lack of direction from Applicants regarding the restoration, increase or stabilization of collagen by decreasing the estrogen content in the skin by the inhibition of aromatase. In light of the above discussion, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Argument

Applicants argue that the original specification is replete with express references to collagen deficiencies and treatments that increase collagen content by the

administration of an aromatase inhibitor (p. 1, lines 4-11; p. 21, lines 13-20, p. 22, line 34 to p. 23, line 12. Applicants acknowledge that their findings are contrary to the official scholarship opinion and assert that their results are supported by experimental studies. Applicants point to the examples regarding the treatment of wrinkles, strias and the results of sun-bathing.

Response

Applicants' argument has been considered but it is not persuasive.

The reference to page 1 is a general statement of the invention. Regarding the disclosure of p. 21 this is a recitation of the prior art. The disclosure on p. 22-23 is the disclosure of the official scholarship.

Argument

Applicants argue that they have shown a reduction to practice in the examples. Applicants assert that the administration of the claimed substances is not particularly difficult to a person having ordinary skill in the art and that the claimed invention can be practiced with routine experimentation.

Response

Applicants' argument has been considered but it is not persuasive.

Regarding the reduction to practice, the content of the examples has been discussed in the rejection *supra*. The administration of the substance is within the ordinary artisan. The point of the rejection is that the claimed invention is contrary to what is disclosed by the prior art (e.g., increased estrogen levels support collagen levels) and the specification does not provide a correlation between anti-aromatase

activity by reduction to practice (that a decrease of estrogen increases collagen levels). Hence, the skilled artisan cannot practice the invention as claimed.

Argument

Applicants assert that as long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim then the enablement requirement is met. Applicants assert that steroidal aromatase inhibitors share a common property that they can effectively penetrate the dermis in order to reach the underlying collagen.

Applicants assert that not everything necessary to practice the invention need be disclosed and what is well-known is best omitted. All that is necessary is that one skilled in the art be able to practice the claimed invention given the level of knowledge and skill in the art. Applicants assert that it is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation.

Applicants assert that the recited aromatase inhibitors are from soya glycines and that since the claimed steroidal aromatase inhibitors share a common sterane core they can effectively penetrate the dermis in order to reach the underlying collagen. Applicants assert that the claimed steroidal aromatase inhibitors can be made by methods known in the art and since the specification discloses a correlation between the application of the claimed steroidal aromatase inhibitors and the claimed effect, the enablement rejections are moot or otherwise accommodated.

Response

Applicants' argument has been considered but it is not persuasive.

The specification does not disclose one method for using the claimed invention that correlates to the entire scope of the invention because the specification does not provide a correlation between anti-aromatase activity an augmentation of collagen.

While it is not necessary to disclose everything related to the invention, the specification does not provide enough disclosure that the skill artisan could practice the claimed invention because the specification does not provide a correlation between anti-aromatase activity and augmentation of collagen. Regarding the dosage, this is disclosed by the specification but again it is unclear how the dosage correlates with inhibition of aromatase that causes an increase in collagen levels.

That steroidal aromatase inhibitor and steranes from soya glycines can penetrate the dermis, this is not disputed but the skilled artisan cannot practice the claimed invention because specification does not provide a correlation between anti-aromatase activity an augmentation of estrogen.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUSAN HANLEY whose telephone number is (571)272-2508. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sue Liu can be reached on 571-272-5539. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Susan Hanley/
Primary Examiner, Art Unit 1653